

An Open-label Phase II Study of Lorvotuzumab mertansine (IMGN901) in CD56  
expressing hematological malignancies

Principal Investigator: Naval Daver, M.D. and Hagop Kantarjian, M.D.

Sponsor: IND office, University of Texas, MD Anderson Cancer Center

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University of Texas  
MD Anderson Cancer Center  
Leukemia Department, Unit 428

## **1.0 OBJECTIVES**

### **1.1 Primary Objectives**

1. To determine the overall response rate of IMGN901 in CD56 expressing hematological malignancies including but not limited to relapsed/refractory acute leukemias, myelofibrosis (MF) refractory to JAK-inhibitor therapy and blastic plasmacytoid dendritic cell neoplasm (BPDCN).

### **1.2 Secondary Objectives**

1. To determine the duration of response, event-free survival (EFS), and overall survival (OS) in patients to IMGN901 in CD56 expressing hematological malignancies including but not limited to relapsed/refractory acute leukemia, MF refractory to JAK-inhibitory therapy and BPDCN.
2. To determine the safety of IMGN901 in CD56 expressing hematological malignancies including but not limited to relapsed/refractory acute leukemia, MF refractory to JAK-inhibitor therapy and BPDCN.

### **1.3 Exploratory Objective**

1. To assess the response rate relative to the quantitative degree of CD56 expression as assessed by flow cytometry.

## **2.0 BACKGROUND**

### **2.1 Acute Myeloid Leukemia (AML)**

#### **2.1.1 Background**

AML is a malignancy of immature granulocytes or monocytes. The malignancy is characterized by accumulation of leukemic blastocytes and blockade of normal bone marrow production resulting in thrombocytopenia, anemia, and neutropenia. There are approximately 13,000 new cases of AML per year in the United States, with an estimated 10,000 deaths occurring in the same time period<sup>1</sup>. Almost all newly diagnosed cases, as well as deaths, will be in adults<sup>2</sup>. Standard treatment for AML includes systemic combination chemotherapy to control bone marrow and systemic disease. Treatment is generally divided into an induction phase, to attain remission, and a maintenance phase<sup>2</sup>. Approximately 60% to 70% of adults with AML can be expected to attain complete remission status following appropriate induction therapy. Remission rates in adult AML are inversely related to age, with an expected remission rate of >65% for those younger than 60 years. Increased morbidity and mortality during induction appear to be directly related to age<sup>3-5</sup>.

#### **2.1.2 Relapsed/ Refractory AML**

Approximately, 30-40% of adults with AML fail to achieve CR with 1 or 2 cycles of induction chemotherapy, and are deemed primary refractory. The outcome of patients with AML who are refractory to induction therapy are dismal, with low response rates to salvage chemotherapy and poor long-term survival<sup>6-8</sup>. We have previously reported a dismal median OS of 3.8 months for patients with AML who are refractory to high dose cytarabine (HiDAC)-containing induction therapy (defined as  $\geq 1\text{ gm/m}^2$  cytarabine per dose)<sup>7</sup>. Salvage therapy in such patient populations yielded a response rate of 18% and median response duration of 9 months.

These results emphasize the need to explore alternate salvage regimens for patients with relapsed/refractory AML. The development of novel and effective anti-AML agents and/or combinations is crucial to improving the outcome of AML.

### **2.1.3 CD56 expression in AML and high-risk myelodysplastic syndrome (MDS)**

Studies at MDACC by Seymour et al and Mann K et al showed CD56 in 22% and 20% of AML/ high-grade MDS and blast-phase CML, respectively<sup>9, 10</sup>. Other groups have noted CD56 expression in 20-24% of AML patients<sup>11-14</sup>. CD56 expression seems to be more frequent in t(8:21) AML: 54% in the series by Seymour et al, 55% in the series by Baer et al, and 68% in the series by Yang et al<sup>9, 15, 16</sup>. In t(8:21) the presence of CD56 expression did not impact the response rate but significantly shortened the CR duration and overall survival. CD56 expression is noted in 10-15% of acute promyelocytic leukemia (APL) and is strongly associated with inferior outcomes<sup>16, 17</sup>. APL patients with CD56 have similar response rates but significantly shortened OS and DFS. CD56 expression has also been associated with extramedullary disease and P-glycoprotein mediated drug resistance<sup>12, 18</sup>. Patients expressing both CD56 and P-glycoprotein seem to do exceptionally poorly.

### **2.1.4 Impact of CD56 expression on outcome**

In non-8:21 and non-APL AML the impact of CD56 on outcome remains poorly defined. Raspaderi et al and Chang et al noted inferior OS in AML patients with CD56 expression<sup>12, 18</sup>. Conversely, Bona et al, Legrand et al, and Junca, et al noted no correlation with response and OS<sup>11, 13, 14</sup>.

Patients with relapsed/refractory AML or high-risk MDS who express CD56 may be suitable candidates for IMGN901.

## **2.2 MF**

### **2.2.1 Background**

MF has an estimated annual incidence of two to three cases per 100,000 persons in the USA<sup>19</sup>. Patients diagnosed with low-risk MF may survive for 15 years or longer, whereas the median life expectancy for intermediate-2 and high-risk

patients is only 3 years and <2 years, respectively<sup>20</sup>. Previous studies estimated the prevalence of MPNs at 75,000+ in the US<sup>21</sup>. Ruxolitinib is the only therapy that is currently approved for the treatment of patients with intermediate and high-risk MF. Two MD Anderson Cancer Center led phase III studies (COMFORT-I, COMFORT-II)<sup>22, 23</sup> showed improvements in spleen size, symptom control and quality of life, resulting in the FDA-approval of ruxolitinib for patients with intermediate or high-risk myelofibrosis. However, the response rate to ruxolitinib single-agent is 42-45%. There is no standard of care post ruxolitinib or JAK inhibitor failure in MF.

### **2.2.2 CD56 expression in MF**

CD56 is expressed on 17-34% of myelocytes and 39-69% of monocytes in MF. In controls, CD 56 was expressed on 0/20 control samples suggesting significantly increased expression in MF<sup>24</sup>.

Patients with MF post JAK 2 inhibitors failure who express CD56 may be suitable candidates for IMGN901

## **2.3 BPDCN**

### **2.3.1 Background**

Recently classified among “acute myeloid leukemia (AML) and related precursor neoplasms” in the 2008 World Health Organization (WHO) classification, BPDCN is a rare subtype of acute leukemia characterized by the clonal proliferation of precursors of plasmacytoid dendritic cells. The precise incidence of BPDCN is difficult to estimate due to constantly changing nomenclature and lack of precise defining criteria prior to the 2008 WHO classification system. BPDCN likely represent 0.7 percent of primary cutaneous skin lymphomas. However, cutaneous lymphoma registries likely underestimate the true incidence of BPDCN because a small but significant proportion of patients present without skin lesions. Tissue biopsies of involved sites reveal uniformly distributed, medium-sized blast cells that co-express CD4 and CD56, dendritic cell-associated markers like CD123, CD45RA, and TCL-1, but lack other lineage-specific markers<sup>25</sup>. Given its recent recognition as a distinct clinico-pathological entity, no standardized therapeutic approach has been established for BPDCN and the optimal therapy remains to be defined. A number of treatment modalities include ALL-like regimens (R-CHOP, HCVAD), AML-like regimens (3+7), hematopoietic stem cell transplant have been studied. The overall survival rate is a dismal 12-14 months<sup>26</sup>.

### **CD56 expression in BPDCN**

The high frequency of CD56 (>80%) expression and need for novel therapies in this disease makes it an ideal target for CD56 antibody therapy.

## **2.4 IMGN901**

### **2.4.1 Introduction**

Lorvotuzumab mertansine (IMGN901) is a humanized immunoglobulin (IgG1) kappa monoclonal antibody, conjugated through a disulfide linker, to the cytotoxic maytansinoid, DM1, with an average of 3.5 molecules DM1 per antibody. The monoclonal antibody is the humanized version of the murine N901 monoclonal antibody engineered to bind specifically with the CD56 antigen, a member of the family of neural cell adhesion molecules (NCAMs). The target CD56 antigen is expressed on the surface of tumor cells of neuroendocrine origin, including small cell lung cancer (SCLC), carcinoid tumors and neuroblastomas, and on neuroectodermal tumors, such as astrocytomas, as well as many multiple myelomas (MM) and ovarian cancers. Additionally, CD56 is expressed on a number of hematological malignancies including acute leukemia, MF, BPDCN, NK-cell leukemia and others.

IMGN901 acts by binding to the target antigen, CD56 on tumor cells and once bound, the conjugate is internalized and DM1 released. Within the cell, DM1 disrupts microtubule assembly, leading to G2/metaphase arrest and ultimately cell death.

### **2.4.2 Nonclinical Pharmacology, pharmacokinetics and toxicology**

#### **2.4.2.1 Pharmacology**

Nonclinical pharmacology studies have demonstrated that the cytotoxicity of IMGN901 is restricted to CD56-positive tumor cell lines and it is active against SCLC, MM, and ovarian cancer as a single agent or in combination with standard-of-care anticancer agents.

#### **2.4.2.2. Pharmacokinetics (PK)**

Absorption, distribution, metabolism and excretion (ADME) studies demonstrate IMGN901 is stable in circulation with an elimination phase half-life of one to two days.

#### **2.4.2.3. Nonclinical Toxicology**

Nonclinical safety evaluation of IMGN901 has focused on studies in cynomolgus monkey due to the lack of cross-reactivity to the antigen in non-primate species. The principal target organ for this species is the peripheral and central nervous system (spinal cord). In a single dose study, single bolus IV infusion of IMGN901 (152 and 456 mg/m<sup>2</sup>) was associated with dose-dependent minimal to mild findings of axonal degeneration of peripheral nerves and spinal cord. Repeat dosing was investigated on a weekly schedule (24 to 228 mg/m<sup>2</sup> for six weeks) and daily schedule (2.4 to 114 mg/m<sup>2</sup> for five days). At the lowest weekly dose tested (24 mg/m<sup>2</sup>) minimal lesions in the spinal cord only were noted. Higher dose levels (> 24 mg/m<sup>2</sup> weekly or daily) were associated with lesions of the peripheral (sciatic and peroneal) and central (cervical, thoracic, and lumbar spinal)

nerves.

The skin was also a target organ, with clinical changes relating to hyperkeratosis (peeling, flaking, cracking, etc.) after a single dose of 456 mg/m<sup>2</sup> or at repeated doses of 114 mg/m<sup>2</sup> weekly or higher. Skin darkening correlated with increased amounts of melanin pigment and prominent melanocytes in the skin were observed following repeat doses of  $\geq 24$  mg/m<sup>2</sup> daily or  $\geq 114$  mg/m<sup>2</sup> weekly.

Changes in markers of hepatic function were limited to rises in transaminases and serum alkaline phosphatase (ALK) in the highest single dose tested (456 mg/m<sup>2</sup>) and transient rises in serum ALK activity with repeat daily doses of 114 mg/m<sup>2</sup>. There were no changes in markers of renal function.

Treatment-related bone marrow suppression, leading to pancytopenia, and effects on the gastrointestinal (GI) system including enteropathy, affecting the small and large intestines, characterized by loss, dilatation and epithelial regeneration of intestinal crypts were seen in animals receiving the highest repeat daily dose of (114 mg/m<sup>2</sup>).

### **2.4.3 Clinical pharmacokinetics and clinical study summaries**

#### **2.4.3.1 Clinical pharmacokinetics**

Preliminary data from patients show that IMGN901 has a rapid clearance, with a half-life of 6 – 14 hours at doses  $\leq 10$  mg/m<sup>2</sup>. Clearance decreases with higher doses ( $\geq 40$  mg/m<sup>2</sup>), with a half-life (t<sub>1/2</sub>) approaching 1 day.

#### **2.4.3.2 Clinical study summaries**

Because of the cytotoxic nature of DM1, studies with IMGN901 in healthy volunteers were neither planned nor conducted.

A total of 369 patients with cancer have been treated with at least one dose of IMGN901 in the clinical development program. Of the 369 patients treated, 198 received IMGN901 as a single agent, and 171 received IMGN901 in combination with other chemotherapeutic agents (either lenalidomide and dexamethasone [n=44] or carboplatin and etoposide [n=127]). The latter study includes a control arm comprised of 47 patients treated with carboplatin and etoposide alone.

##### **2.4.3.2.1. Single agent IMGN901**

IMGN901 has been investigated as a single agent in patients with SCLC (Study 001), CD56-positive solid tumors (Study 002) and MM (Study 003); all three of these studies are complete<sup>27, 28</sup>. A summary of available clinical data obtained in approximately 198 patients receiving single-agent IMGN901 (Studies 001, 002, 003) as of 31 March 2014, demonstrate the

following:

- ☐ Most treatment-related treatment-emergent adverse events (TEAEs) experienced with single-agent IMGN901 were low grade (Grade 1 or 2) and reversible. Treatment-related TEAEs occurring in  $\geq 20\%$  of patients, in descending order of frequency, included neuropathy peripheral (31%), headache (30%), fatigue (29%), and nausea (27%).
- ☐ As noted above, treatment-related headache was commonly reported (30%), but most events were mild to moderate. Early in the clinical development program, severe, meningitis-like symptoms associated with headaches were reported; however, similar events have not been observed since implementation of a slowed infusion rate and routine steroid prophylaxis.
- ☐ While the overall incidence of peripheral neuropathy and paraesthesia, irrespective of relationship to study treatment, was 33% and 9%, respectively, the Grade 3 incidence was low (3% and  $< 1\%$  respectively), and there were no Grade 4 reports.

The majority of changes in hematologic laboratory values observed with single-agent IMGN901 were mild to moderate. Across the three single-agent Phase 1 studies, at least one Grade 3 or Grade 4 hematologic abnormality was reported for 35% and 1% of patients, respectively. The most common Grade 3 abnormality was a decrease in lymphocyte count (29%). Most of the changes in chemistry laboratory values observed with single-agent IMGN901 were Grade 1 or 2 in intensity. At least one Grade 3 or Grade 4 abnormality was reported in 46% and 8% of patients, respectively. The most common Grade 3 and/or 4 abnormalities were hyperglycemia (18%, all Grade 3) and gamma-glutamyl transferase (GGT) increased (12%, 10% Grade 3 and 2% Grade 4).

- ☐ Skin changes noted in preclinical models have not been observed in the clinic.

#### **2.4.3.2.2 IMGN901 in combination regimens**

Additionally, IMGN901 has been investigated as part of a combination regimen in patients with MM in combination with lenalidomide and dexamethasone (Study 0005, closed to accrual) and in patients with SCLC in combination with carboplatin and etoposide (Study 0007, closed to accrual)<sup>29</sup>.

#### **A. IMGN901 in Combination with Lenalidomide and Dexamethasone (Study 0005)**

- A total of 44 patients with relapsed or relapsed/refractory MM have been treated with lenalidomide (25 mg)/dexamethasone (40 mg) plus IMGN901 at doses of 75 mg/m<sup>2</sup> (n=34), 90 mg/m<sup>2</sup> (n=4), or 112 mg/m<sup>2</sup> (n=6). All patients (n=44) experienced at least one TEAE, with all also having at least one TEAE that was considered by the Investigator to be treatment-related. Overall, 91%, 21%, and 5% of patients have experienced at least one Grade 3, Grade 4, or Grade 5 event, respectively.
- Overall, the most common types of TEAEs were in the SOC of nervous system disorders (91%), with neuropathy peripheral being the most common AE (68%) and the most common treatment-related AE (66%). Other common TEAEs included fatigue (50%), diarrhea (43%), nausea (36%), pyrexia (34%), and cough (32%).
- Not unexpectedly in this population of patients with a hematologic malignancy, all patients (n=44) experienced at least one hematologic laboratory abnormality. The most common Grade 3 or 4 hematologic abnormality was decreased hemoglobin, which was reported in all patients. The incidence of Grade 3 and 4 decreased hemoglobin was 25% and 2%, respectively. Decreased lymphocyte count was reported in 77% of patients, with Grade 3 and Grade 4 incidences of 32% and 14%, respectively. Fifty-seven percent and 46% of patients experienced decreased platelet count and neutrophil count, respectively, which may reflect effects of lenalidomide and dexamethasone.
- Dose-limiting toxicities (DLTs) were reported for six patients (18%) at the 75 mg/m<sup>2</sup> dose level, and included Grade 2 peripheral neuropathy (three patients), Grade 2 tremor (one patient), and the following Grade 3 AEs in one patient each: tumor lysis syndrome and alanine aminotransferase (ALT) elevation.

## **B. IMGN901 in Combination with Carboplatin and Etoposide (Study 0007)**

### **Phase 1**

In Phase 1 of Study 0007, a total of 33 patients with advanced solid tumors, including SCLC, have been enrolled and treated with IMGN901, including six patients treated with IMGN901 60 mg/m<sup>2</sup>, carboplatin (AUC6) and etoposide; six patients treated with IMGN901 75 mg/m<sup>2</sup>, carboplatin (AUC6) and etoposide; three patients treated with IMGN901 75 mg/m<sup>2</sup>, carboplatin (AUC5) and etoposide; six patients treated with IMGN901 90 mg/m<sup>2</sup>, carboplatin (AUC5) and etoposide; and twelve patients treated with IMGN901 112 mg/m<sup>2</sup>, carboplatin (AUC5) and etoposide.



□ All patients (n=33) experienced at least one TEAE with most TEAEs being mild or moderate (Grade 1 or 2) in intensity and reversible. For most patients (97%), at least one TEAE was considered by the Investigator to be study treatment related. Treatment-related TEAEs occurring in > 10% of patients included anemia (55%), neuropathy peripheral (52%), thrombocytopenia (49%), fatigue (46%), nausea (33%), alopecia and neutropenia (each 27%), leukopenia (24%), lymphocyte count decreased and white blood cell count decreased (each 21%), vomiting (18%), decreased appetite, febrile neutropenia, and neutrophil count decreased (each 15%), and diarrhea and lymphopenia (12% each).

□ All three patients treated with IMGN901 at a dose of 75 mg/m<sup>2</sup>, with carboplatin at an AUC 6 reported DLTs related to myelosuppression, including Grade 3 or 4 febrile neutropenia (two patients), Grade 4 thrombocytopenia (two patients), and Grade 4 granulocytopenia (one patient). Therefore, the sponsor and investigators agreed to explore escalating doses of IMGN901 in combination with a reduced dose of carboplatin dose (AUC5). Escalation with IMGN901 continued to the maximum planned dose of (112 mg/m<sup>2</sup>). As only two of 12 patients reported a DLT at the 112 mg/m<sup>2</sup> dose level, including Grade 3 lobar pneumonia and Grade 4 thrombocytopenia in one patient each, this dose was declared the recommended Phase 2 dose (RP2D), and this dose level was initially employed in the Phase 2 portion of Study 0007. The IMGN901 dose subsequently has been reduced to 90 mg/m<sup>2</sup> due to an increased frequency of peripheral neuropathy among patients receiving IMGN901 at 112 mg/m<sup>2</sup>.

## Phase 2

In Phase 2 of Study 0007, 94 patients with SCLC extensive disease have received IMGN901 in combination with carboplatin and etoposide (Arm 1); of these 94 patients, 50 received IMGN901 at a dose of 112 mg/m<sup>2</sup> and 44 received IMGN901 at a dose of 90 mg/m<sup>2</sup>. Additionally, 47 patients have received carboplatin and etoposide alone (Arm 2).

□ In March 2013, an interim aggregate analysis of safety data from Study 0007 revealed an increased frequency of peripheral neuropathy when IMGN901 is administered in combination with carboplatin and etoposide. A Data Monitoring Committee (DMC) meeting was held to review available safety data and the sponsor's revised dose modification guidelines for patients experiencing peripheral neuropathy. The DMC concurred with the sponsor's revised dose modification guidelines and recommended to lower the IMGN901 dose from 112 mg/m<sup>2</sup> to 90 mg/m<sup>2</sup>. This change was implemented in April 2013. As noted above, of the 94 patients treated in Arm 1, 50 received IMGN901 112 mg/m<sup>2</sup> and 44 received IMGN901 90 mg/m<sup>2</sup>.

Based on data through 31 March 2014, the rate of peripheral neuropathy events was 79% in Arm 1 versus 13% in Arm 2. Comparison of the rate of peripheral neuropathy events by IMGN901 dose in Arm 1 showed that lowering the dose of IMGN901 to 90 mg/m<sup>2</sup> and institution of management procedures for such events was associated with a lower incidence of peripheral neuropathy events of 71% compared to 86% at the higher dose of 112 mg/m<sup>2</sup>. Furthermore, the Grade 3 incidence of peripheral neuropathy events was lower with IMGN901 90 mg/m<sup>2</sup> than with 112 mg/m<sup>2</sup> (11% versus 36%, respectively). No Grade 4 peripheral neuropathy events were reported.

Review of TEAEs by study arm, regardless of IMGN901 dose, showed that TEAEs occurring at a  $\geq 10\%$  higher incidence in Arm 1 than in Arm 2 included neuropathy peripheral (61% versus 9%); fatigue (50% versus 30%); asthenia (32% versus 21%); constipation (32% versus 19%); diarrhea (31% versus 17%); paraesthesia (22% versus 4%); insomnia (19% versus 9%); and dyspepsia (14% versus 0%).

□ Review of TEAEs by IMGN901 dose in Arm 1 showed that TEAEs occurring at a  $> 10\%$  higher incidence with IMGN901 112 mg/m<sup>2</sup> than with 90 mg/m<sup>2</sup> included neutropenia (58% versus 46%); nausea (50% versus 36%); alopecia (38% versus 18%); paraesthesia (30% versus 14%); arthralgia (24% versus 11%); white blood count decreased (14% versus 2%); and mucosal inflammation (20% versus 7%).

□ Most patients (95%) in the IMGN901 arm experienced at least one study treatment-related TEAE (for all grades). Study treatment-related TEAEs occurring in  $> 10\%$  of IMGN901-treated patients included neuropathy peripheral (61%); neutropenia (46%); fatigue (43%); anemia (40%); nausea (35%); thrombocytopenia (28%); decreased appetite (26%); asthenia and diarrhea (each 25%); paraesthesia (22%); alopecia (16%); neutrophil count decreased and platelet count decreased (each 14%); hypomagnesemia (13%); and arthralgia, constipation, and vomiting (each 12%).

Thirty-one (33%) IMGN901-treated patients experienced a total of 52 SAEs that were considered by the Investigator to be at least possibly related to study drug, most commonly including febrile neutropenia (7%); neutropenia, neuropathy peripheral; pneumonia, and septic shock (each 4%); and neutropenic sepsis and sepsis (each 3%).

The incidence of infectious serious adverse events including fatal outcome was higher in Arm 1 (16%) compared to Arm 2 (11%). A majority of these events occurred within the first 2 cycles (42 days) of

study treatment. The most common infectious events in Arm 1 were pneumonia (6%) and septic shock (5%). The overall rate of death from a serious infectious event was 11% for Arm 1 compared to 4% for Arm 2.

Sixteen (17%) patients in Arm 1 of Study 0007, Phase 2, died on-study (within 28 days of last study treatment). The causes of death among these 16 patients were pneumonia (four patients); sepsis (three patients); and acute severe respiratory failure, cardiac arrest, disease progression, gastrointestinal bleeding, hypotension, pleural effusion, pyrexia, septic shock and suicide (one patient each). The cause of death was considered to be study treatment-related for eight (9%) patients, including sepsis (three patients); pneumonia (two patients), and hypotension, pyrexia and septic shock (one patient each).

Further details can be found in the IMGN901 investigator brochure (Appendix C), which contains comprehensive pharmacology, toxicology, pharmacokinetics, pharmacodynamics, metabolism, preclinical, and clinical efficacy and safety data information

### 3.0 STUDY DESIGN:

3.1 The study will be a phase II, single-institution, open-label, non-randomized, parallel group clinical trial. The study will include three separate cohorts to be enrolled simultaneously. A response and toxicity summary for each treatment cohort (1, 2 and 3) will be submitted to the IND Medical Monitor per the guidelines found in the statistical section 12.0.

1. **CD56 expressing hematological malignancies (Cohort 1):** Patients with confirmed CD56 expressing hematological malignancies including but not limited to AML, high-risk MDS, natural-killer leukemia, acute lymphoblastic leukemia, accelerated and blast-phase CML who have failed prior therapy or for which no standard therapy exists. Relapsed/ refractory status defined by the failure of at least one prior cycle of chemotherapy (including but not limited to cytotoxic chemotherapy, hypomethylator therapy, FLT3-inhibitor therapy, stem cell transplant or stem cell therapy investigational therapy, targeted therapy, immune-based therapy, and others).
2. **MF (Cohort 2):** To be eligible for this cohort patients must have intermediate or high-risk MF (either primary MF, post-polycythemia MF, or post-essential thrombocythemia MF), have confirmed CD56 expression and have been on ruxolitinib or JAK-inhibitor therapy for at least 12 weeks and deemed refractory or sub-optimal responders in the opinion of the treating physician.
3. **BPDCN (cohort 3):** Patients with a pathological diagnosis of BPDCN and

confirmed CD56 expression.

#### **4.0 PATIENT SELECTION**

Patients must have baseline evaluations performed prior to the first dose of study drug and must meet all inclusion and exclusion criteria. Results of all baseline evaluations, which assure that all inclusion and exclusion criteria have been satisfied, must be reviewed by the Principal Investigator or his/her designee prior to enrollment of that patient. In addition, the patient must be thoroughly informed about all aspects of the study, including the study visit schedule and required evaluations and all regulatory requirements for informed consent. The written informed consent must be obtained from the patient prior to initiating treatment or any study-specific procedures. The following criteria apply to all patients enrolled onto the study unless otherwise specified.

##### **4.1 Inclusion Criteria**

1. Patients with CD56 expressing hematological malignancy, as follows:
  - A. Cohort 1: CD56 expressing hematological malignancies including but not limited to AML, high-risk MDS, natural-killer leukemia, acute lymphoblastic leukemia, accelerated and blast-phase CML who have failed prior therapy or for which no standard therapy exists
  - B. Cohort 2: Patients with MF (either primary MF, post-polycythemia MF, or post-essential thrombocythemia MF) and CD56 expression who have been on ruxolitinib or JAK-inhibitor therapy for at least 12 weeks and deemed refractory or sub-optimal responders in the opinion of the treating physician
  - C. Cohort 3: Patients with pathological diagnosis of BPDCN with CD56 expression (frontline and relapsed/refractory).
2. Any level of CD56 expression will be considered sufficient for enrollment on this study.
3. Prior therapy with hydroxyurea, chemotherapy, biological or targeted therapy (e.g. FLT3 inhibitors, other kinase inhibitors), or hematopoietic growth factors is allowed.
4. Age  $\geq 18$  years
5. Eastern Cooperative Oncology Group (ECOG) Performance Status  $\leq 2$
6. Adequate organ function: total bilirubin  $\leq 2$  times upper limit of normal ( $\times$  ULN) ( $\leq 3 \times$  ULN if considered to be due to leukemic involvement or Gilbert's syndrome); aspartate aminotransferase (AST) or alanine aminotransferase (ALT)

$\leq 2.5 \times \text{ULN}$  ( $\leq 5.0 \times \text{ULN}$  if considered to be due to leukemic involvement);  
serum creatinine  $\leq 2 \times \text{ULN}$ , amylase and lipase  $\leq 2 \times \text{ULN}$ .

7. In the absence of rapidly progressing disease and after discussion with the PI, the interval from prior treatment to time of IMGN901 administration will be at least 2 weeks or at least 5 half-lives for cytotoxic/noncytotoxic agents. The half-life be based on published pharmacokinetic literature (abstracts, manuscripts, investigator brochure's, or drug-administration manuals) and will be documented in the protocol eligibility document. For prior monoclonal antibody therapy the interval from prior monoclonal antibody treatment to time of IMGN901 administration will be at least 2 weeks. The use of chemotherapeutic or anti-leukemic agents other than hydroxyurea (as defined in the protocol) is not permitted during the study with the exception of intrathecal (IT) therapy for patients with controlled CNS leukemia at the discretion of the PI. Hydroxyurea is allowed prior to the initiation of IMGN901 and during the first 3 cycles, either prior to or concomitantly with IMGN901 administration to control leukocytosis.
8. Women of childbearing potential must practice contraception. Females of childbearing potential: Recommendation is for 2 effective contraceptive methods during the study. Adequate forms of contraception are double barrier methods (condoms with spermicidal jelly or foam and diaphragm with spermicidal jelly or foam), oral, depo provera, or injectable contraceptives, intrauterine devices, and tubal ligation. Male patients with female partners who are of childbearing potential: Recommendation is for male and partner to use at least 2 effective contraceptive methods, as described above, during the study.
9. Females must be surgically or biologically sterile or postmenopausal (amenorrheic for at least 12 months) or if of childbearing potential, must have a negative serum or urine pregnancy test within 72 hours before the start of the treatment
10. Patients must provide written informed consent.
11. Women of childbearing potential must agree to use an adequate method of contraception during the study and until 3 months after the last treatment. Males must be surgically or biologically sterile or agree to use an adequate method of contraception during the study until 3 months after the last treatment.

Adequate methods of contraception include:

- Total abstinence when this is in line with the preferred and usual lifestyle of the patient. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.
- Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study

treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment

- Male sterilization (at least 6 months prior to screening). For female patients on the study, the vasectomized male partner should be the sole partner for that patient
- Combination of any of the two following (a+b or a+c or b+c)
  - a) Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
  - b) Placement of an intrauterine device (IUD) or intrauterine system (IUS)
  - c) Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository

In case of use of oral contraception, women should have been stable on the same pill before taking study treatment.

**Note:** Oral contraceptives are allowed but should be used in conjunction with a barrier method of contraception due to unknown effect of drug-drug interaction.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

## 4.2 Exclusion Criteria

1. Patients with known allergy or hypersensitivity to IMGN901.
2. Patients who have previously been treated with IMGN901.
3. Patients with symptomatic CNS leukemia or patients with poorly controlled CNS leukemia.
4. Peripheral neuropathy >grade 2.
5. Active or clinically symptomatic chronic pancreatitis or disease affecting pancreas.
6. Neurologic disease including multiple sclerosis, Eaton-Lambert syndrome, demyelination.

7. Significant cardiac disease including myocardial infarction or unstable angina within 6 months, uncontrolled hypertension despite medical therapy (defined as blood pressure >160/110 in spite of adequate medical therapy), active and uncontrolled congestive heart failure NYHA class III/IV, stroke within preceding 6 months.
8. Patients with known Human Immunodeficiency Virus seropositivity will be excluded.
9. Known to be positive for hepatitis B by surface antigen expression. Known to have active hepatitis C infection (positive by polymerase chain reaction or on antiviral therapy for hepatitis C within the last 6 months). Known to be active CMV infection or herpes zoster infection.
10. Pregnant or breast feeding (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive  $\beta$ -HCG laboratory test.
11. Patients with any concurrent severe and/or uncontrolled medical condition or active uncontrolled systemic infection as determined by the investigator.
12. Patients who have had any major surgical procedure within 14 days of Day 1.
13. Patients unwilling or unable to comply with the protocol.

## **5.0 TREATMENT PLAN:**

### **5.1 Schedule**

All patients will be registered through CORE.

IMGN901 will be administered intravenously at a dose of 100 mg/m<sup>2</sup> on day 1 and 8 of a 21-day cycle. All doses may be +/- 2 days. This dose and schedule is below the established MTD of single agent IMGN901 in multiple myeloma studies. In the myeloma studies by Chanan-Khan et al. the MTD of single-agent IMGN901 was established to be 112mg/m<sup>2</sup> administered via intravenous (IV) infusion once weekly for two weeks every three weeks<sup>28</sup>.

For further details regarding dose-calculation of IMGN901, preparation and dispensing of IMGN901, administration of IMGN901, patient monitoring during infusion and treatment of IMGN901 related infusion reactions please see the dosing procedure manual (Appendix D).

- 5.1.1.1** Cycles may be started early (but not earlier than day 19) for patients with active leukemia (i.e. bone marrow blasts > 5% or peripheral or peripheral blood blast >5%) if judged in the best interest of the patient.
- 5.1.1.2** Subsequent cycles may be delayed at the discretion of the investigator for recovery of drug-related toxicity or other medical conditions (e.g. infections). Delays in start of subsequent cycles greater than 56 days will be acceptable only for patients who are deriving clinical benefit and after discussion with the principal investigator of potential risk/benefit ratio.
- 5.1.1.3** Subsequent courses may be administered regardless of peripheral blood counts during the first 4 cycles and/or if bone marrow blasts >5% or peripheral blood blast >5%). If the peripheral counts do not recover but there is evidence of active leukemia (i.e. bone marrow blasts >5% or peripheral blood blast >5%), subsequent cycles can be administered at the discretion of the treating physician not earlier than 19 days after the prior cycle..
- 5.1.1.4** If prolonged myelosuppression (more than 56 days) with evidence of a hypocellular marrow (marrow cellularity less than 5% without evidence of leukemia) is observed, IMGN901 will be discontinued. If the peripheral counts do not recover but there is evidence of residual leukemia in the bone marrow, subsequent cycles can be administered at the discretion of the treating physician not earlier than 19 days after the prior cycle. This will apply both after 4 cycles and after remission is achieved. Delays in start of subsequent cycles greater than 56 days will be acceptable only for patients who are deriving clinical benefit and after discussion with the principal investigator of potential risk/benefit ratio.
- 5.1.1.4** For patients who discontinue therapy, the reason for treatment discontinuation will be captured.

## **5.2 IMGN901 administration**

For use in clinical trials, IMGN901 is supplied by Immunogen, Inc. as single-use vials in strengths of 100 mg and is formulated for intravenous (IV) administration. IMGN901 drug product is a clear, colorless liquid formulation that contains the bulk active drug substance (huN901 antibody conjugated to DM1) and other inactive ingredients (excipients). The drug product formulation is 5.0 mg/mL



IMGN901, 10 mM succinate, 250 mM glycine, 0.5% (w/v) sucrose, 0.01% (w/v) Polysorbate 20, pH 5.5. The final product vial is stored at 2 to 8°C (36 to 46°F). Details of IMGN901 administration are provided in the IMGN901 Pharmacy Manual (Appendix D). Variations in infusion times of IMGN901 due to minor differences in IV bag overfill/underfill and institutional procedure on flushing chemotherapy lines will not result in protocol deviation. All infusion times are considered approximate.

Unused or expired IMGN901 will be safely disposed according to MD Anderson pharmacy standard guidelines.

### **5.3 Duration of Therapy**

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

1. Clinically significant progressive disease
2. Intercurrent illness that prevents further administration of treatment,
3. Patient request
4. General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
5. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.

**5.3.1** It is planned that up to a total of 12 cycles of therapy will be administered for patients deriving benefit from this regimen. Continuation of therapy for patients completing 12 cycles of therapy may be considered on a case-by-case basis after discussion with the principal investigator.

**5.3.2** A minimum of 1 full course [defined as the administration of at least 2 doses of IMGN901 on days 1 (+/-2 days) and 8 (+/-2 days) of the 21 day cycle] will be required for a patient to be considered as having received an adequate trial to evaluate efficacy. All patients who receive two doses of IMGN901 during the first cycle will be evaluable. All patients receiving at least one dose of any of IMGN901 will be considered evaluable for toxicity.

### **5.4 Supportive care**

Supportive care measures including blood products, infection prophylaxis and growth factors will be administered according to institutional and Leukemia Department guidelines.

## 5.5 Concomitant medications

If considered necessary for the subject's wellbeing, drugs for concomitant medical conditions or for symptom management may be given at the discretion of the investigator. The investigator's decision to authorize the use of any drug other than study drug should take into account subject safety, the medical need, the potential for drug interactions, the possibility for masking symptoms of a more significant underlying event, and whether use of the drug will compromise the outcome or integrity of the study.

Recommendations with regard to specific types of concomitant therapies, supportive care, diet and other interventions are as follows:

Concomitant medications are recommended as prophylaxis for nausea, vomiting, and infections, and are allowed for managing myelosuppression as shown in Table 1. Myelosuppression is expected in patients with AML due to underlying disease, as well as due to the therapy (IMGN901), or both. Most patients have neutropenia, thrombocytopenia, or both at study entry. Significant or life-threatening myelosuppression may be managed with growth factor support including G-CSF, GM-CSF and platelet growth factors and erythropoietin/darbopoetin/blood transfusion according to institutional standard of care, American Society of Clinical Oncology (ASCO) Practice Guidelines, and/or NCCN Practice Guidelines.

Infections secondary to myelosuppression are common in patients with AML, and may be related to underlying disease, chemotherapy, or both. Therefore, the use of prophylactic antibiotics, antifungal agents, and antiviral agents is recommended according to institutional standards.

Since the effect of IMGN901 may be delayed, patients with high WBC counts may receive hydroxyurea prior to study entry. Hydroxyurea is allowed before the start of study therapy and during the first 3 cycles to control leukocytosis. Hydroxyurea use would be recorded in the CRF. Concurrent therapy for CNS prophylaxis or continuation of therapy for controlled CNS disease is permitted. With the exception of these agents, concomitant systemic chemotherapy or radiation therapy is not permitted. Subjects are not allowed to participate concurrently in any other therapeutic clinical study to treat the primary disease process. Supportive care and laboratory protocol participation is allowed.

Subjects may be receiving systemic corticosteroids (daily doses  $\leq 10$  mg of prednisone or equivalent if indicated for adrenal replacement or antiemetic therapy), topical, or inhaled corticosteroids at study enrollment. They may receive systemic, topical, inhaled, or enteric corticosteroids while on study without limitation if they develop conditions that require corticosteroid therapy; such subjects are not required to discontinue study participation.

All ongoing medications and therapies (including herbal products, nutritional supplements, and nontraditional medications) at screening will be considered prior medications. Concomitant medication data will not be collected or entered into the case report form other than hydroxyurea and cytarabine; however, the subject's medication record will contain a list of concomitant medications. If a prohibited medication is inadvertently administered/ taken by the patient, the patient may remain on study as long as the prohibited medication is discontinued as soon as feasible. If a prohibited medication is considered essential for the patient well being, continuation on study with concomitant administration of such medication(s) will need to be discussed with and approved by principal investigator.

**Table 1: Instructions for the use of concomitant medications and therapies**

Category of Use	Medication	Comment on Use	Restriction on Use
Recommended	Prophylactic antibiotics, antifungal agents, and antiviral agents	Strongly encouraged	None
	Antiemetic agents	According to standard of care at MDACC	None
Allowed	Oral allopurinol or rasburicase	At investigators discretion	None
	Leukapheresis	According to standard of care at MDACC	Before induction 1 day 1 only
	Red blood cell transfusion	According to standard of care at MDACC	None
	Platelet transfusion	According to standard of care at MDACC	None
	White blood cell transfusion	At investigators discretion according	None

		to standard of care at MDACC	
	Myeloid growth factors or platelet growth factor	At investigators discretion according to standard of care at MDACC	None
	Erythropoietin or darbepoetin	At investigators discretion	None
	Any other medication for supportive care	At investigators discretion according to standard of care at MDACC	None

## 6.0 DOSING DELAYS/DOSE MODIFICATIONS

Table 2: Dosing schema

Dose level	IMGN901
0	100 mg/m <sup>2</sup> day 1,8
-1	80 mg/m <sup>2</sup> day 1,8
-2	60 mg/m <sup>2</sup> day 1, 8
-3	40 mg/m <sup>2</sup> day 1, 8

### 6.1 Toxicity Directly Attributable to Study Drug

Patients experiencing unacceptable clinically significant toxicity directly attributable to the IMGN901 should temporarily stop treatment according to the guidelines in the dose adjustment schema.

### 6.2 Toxicity Grading

Toxicity grading will be according to the NCI CTCAE, version 4.0 (Appendix F). To prevent unnecessary morbidity, the following guidelines for dose adjustment for drug-related toxicities are recommended.

### 6.3 Dose Reductions

**Dose reductions** for non-hematologic toxicity possibly related to study drugs should be performed according to table 3 below.

Toxicity	Grade	Actions
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Non-hematological (excludes myalgia/arthralgia responding to treatment, inadequately treated vomiting and diarrhea, or electrolyte abnormalities unless not responding to optimal supplementation)	3 or 4	Hold therapy until recovery to Grade $\leq 1$ , then re-start with a one dose level reduction. If toxicity recurs, hold therapy until recovery to grade $\leq 1$ , then re-start and reduce one additional dose level. Patients requiring dose reductions below dose level -3 will be taken off-protocol.
Non-hematological (excludes myalgia/arthralgia responding to treatment, inadequately treated vomiting and diarrhea, or electrolyte abnormalities unless not responding to optimal supplementation)	Persistent 2 considered clinically significant or upon patient's request	Consider holding therapy until recovery to Grade $\leq 1$ , then re-start and reduce one dose level. If toxicity recurs again, therapy may be held until recovery to grade $\leq 1$ , then re-start and reduce one additional dose level. Patients requiring dose reductions below dose level -3 will be taken off-protocol.

**Table 3. Dose adjustments for non-hematologic drug-related AEs, clinically significant in the opinion of the investigator**

- 6.3.1** Peripheral neuropathy: For peripheral neuropathy hold therapy for grade 2 and then restart at lower dose once neuropathy subsides to grade 1. For grade 1 peripheral neuropathy do not hold dose but consider administering the subsequent dose at one dose level reduction.
- 6.3.2** Hepatotoxicity: A reduction in the dose of IMGN901 is recommended in cases of drug-related hepatotoxicity, as follows: Patients with any instance of drug-related grade 4 hepatotoxicity will permanently discontinue therapy with IMGN901.

Dose-modifications for drug-related increased serum transaminases (AST/ALT)

Grade 2(>3.0 to $\leq 5$ x ULN)	Grade 3(>5 to $\leq 20$ x ULN)	Grade 4 (>20 x ULN)
Treat at same dose level	Do not administer IMGN901 until AST/ALT recovers to Grade $\leq 2$ , and then reduce one dose level.	Permanently discontinue IMGN901.

Dose-modifications for drug-related hyperbilirubinemia

Grade 2(>1.5 to ≤3 x ULN)	Grade 3(>3 to ≤10 x ULN)	Grade 4 (>10 x ULN)
Do not administer IMGN901 until total bilirubin recovers to Grade ≤ 1, and then treat at same dose level.	Do not administer IMGN901 until total bilirubin recovers to Grade ≤ 1, and then treat at same dose level.	Permanently discontinue IMGN901.

Permanently discontinue IMGN901 treatment in patients with drug-related serum transaminases  $> 3 \times \text{ULN}$  and concomitant total bilirubin  $> 2 \times \text{ULN}$ .

Permanently discontinue IMGN901 in patients diagnosed with drug-related nodular regenerative hyperplasia (NRH)

**6.3.3** Patients in whom the toxicity occurs or persists beyond the planned completion of drug administration for the cycle will have the dose reductions implemented in subsequent cycles provided the toxicity has resolved as specified in the table above.

**6.3.4** If the criteria to resume treatment are met, the subject should restart treatment at the next scheduled time point per protocol. However, if the treatment is delayed past the next scheduled time point per protocol, the next scheduled time point will be delayed until dosing resumes.

## 6.4 Myelosuppression

- Patients with acute leukemia's usually present with abnormal peripheral blood counts at the time therapy is started and myelosuppression is an expected event during the course of therapy for acute leukemia's. Thus, no dose adjustments or treatment interruptions for myelosuppression will be planned for the first 4 cycles and/or in the presence of any residual leukemia. After that, treatment interruptions and dose adjustments may be considered according to the following guidelines only when there is no evidence of active leukemia.

- Patients with a complete response (e.g., only if  $<5\%$  blasts in the bone marrow or cytopenias not considered to be related to leukemia) and pre-cycle counts of neutrophils  $>1 \times 10^9/\text{L}$  and platelets  $>50 \times 10^9/\text{L}$  who have sustained low counts of neutrophils  $<0.5 \times 10^9/\text{L}$  or a platelet count  $<20 \times 10^9/\text{L}$  for more than 2 consecutive weeks in the current cycle, may have the

treatment with IMGN901 interrupted at the discretion of the treating physician after discussing with the PI until neutrophils recover to  $\geq 0.5 \times 10^9/\text{L}$  and platelets to  $\geq 30 \times 10^9/\text{L}$ .

- If there are persistent peripheral blood blasts, or the bone marrow shows  $>5\%$  blasts or any evidence of leukemia, treatment may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions of IMGN901 in these patients should be considered on an individual case and discussed with the PI.
- Patients with a response (no evidence of leukemia) and pre-cycle counts of neutrophils  $<1 \times 10^9/\text{L}$  and platelets  $<50 \times 10^9/\text{L}$  may be continued regardless of neutrophil and platelet count with supportive care as needed. Dose-interruptions in these patients should be considered on an individual case and discussed with the PI.

**6.4 Modifications of dose schedules other than the above** will be allowed within the following guidelines:

- 6.4.1** Further dose reductions can be made to keep clinically significant IMGN901-related toxicity grade  $\leq 2$ . However, the lowest acceptable dose is 40 mg/m<sup>2</sup> on days 1 and 8.
- 6.4.2** Dose adjustments by more than 1 dose level at a time (e.g., from 100 mg/m<sup>2</sup> to 60 mg/m<sup>2</sup> mg on days 1 and 8) can be considered when judged in the best interest of the patient (e.g., neutropenia with sepsis, bleeding requiring platelet transfusions) when toxicity has resolved. The reason for this reduction will be discussed with the PI or Co PI and documented in the medical record.
- 6.4.3** A patient who has had a dose reduction because of any of the reasons mentioned above may have their dose escalated provided the toxicity requiring dose adjustments has resolved to  $\leq$  grade 1. Escalation will be made by 1 dose-level increment only, and not more frequent than every 21 days.
- 6.4.4** Treatment interruptions and dose modifications other than the ones mentioned above can be considered after discussion with the PI and proper documentation of the rationale.
- 6.4.5** All dose adjustments will be made according to the protocol unless

otherwise specified.

## 7.0 AGENT FORMULATION AND PROCUREMENT (Appendix D)

**7.1 Appearance:** 5 mg/mL Formulation: Clear, colorless solution, essentially free from visible particulate matter

**7.2 Active Ingredient:** huN901-DM1

**7.3 Purity:**  $\geq 95\%$  as determined by size-exclusion High Performance Liquid Chromatography (HPLC)

**7.4 Molecular Weight:** About 146,145 Da (deglycosylated mass of huN901 antibody as determined by mass spectrometry) plus  $[737.5]n$  (mass of attached DM1 with linker,  $n = \sim 3.5$  drug linked per antibody)

**7.5 Container/Closure:** Single use 20 mL/20 mm Type I clear glass vials, with a 20 mm coated stopper.

**7.6 Formulation and strength:** IMGN901 is a solution for IV infusion supplied in single use vials at a protein concentration of 5.0 mg/mL in buffered solution (pH 5.5). The drug product formulation is 5.0 mg/mL IMGN901, 10 mM succinate, 250 mM glycine, 0.5% (w/v) sucrose, 0.01% (w/v) Polysorbate 20, pH 5.5. The final product is presented in 20 mL clear glass, sterile vials, Type I. Each vial is sealed with a Flurotec®-coated stopper. Each vial contains 20 mL IMGN901 solution for infusion.

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Only clear, colorless solutions should be administered. If the IMGN901 solution is not clear and colorless it should be returned to ImmunoGen. Patients should be observed for at least one hour after completion of each infusion or as instructed in the study specific protocol.

**7.7 Storage and handling:** The product should not be shaken or frozen; it should be stored at 2 to 8°C (36 to 46°F) and allowed to equilibrate to ambient temperature for 15 minutes before use. The shelf-life at 2 to 8°C (36 to 46°F) is provided on the vial-label, or is provided on the Certificate of Analysis provided to the site with each shipment of IMGN901 vials.

**7.8 Preparation and premedications:** IMGN901 will be administered per dose and schedule relevant to each investigational study. IMGN901 should be prepared by a pharmacist or other appropriately licensed and authorized personnel and administered as described in the study specific protocol or pharmacy manual.



The following steps should be carried out in a laminar flow hood, using aseptic technique throughout:

- ☐ Take the required number of vials from cold storage 15 minutes before required to allow solution to reach ambient temperature (18 to 25°C).
- ☐ Draw up the appropriate volume of IMGN901 solution into a suitably sized sterile syringe.
- ☐ Transfer the required volume of IMGN901 to a sterile infusion bag or syringe.
- ☐ Note: (5 mg/mL concentration) is diluted 1:1 in normal saline or 5% dextrose prior to adding to the infusion bag.
- ☐ Do not leave the prepared drug in direct sunlight.

Administer IMGN901 IV infusion within eight hours of preparation using a low protein binding 0.22-micron filter.

In early studies of IMGN901, patients reported headache with aseptic meningitis-like symptoms. Since the introduction in protocols of a corticosteroid-based premedication, there have been no further reports of these AEs in the later studies. Premedication with hydrocortisone 100 mg IV or equivalent corticosteroid-based agent should be implemented prior to every infusion of IMGN901.

**7.9 Drug Infusion:** The drug will be administered via an intravenous tubing set with a 0.2 micron in-line filter. In the case that an in-line filter is unavailable, a 0.2 micron filter unit may be attached to the administration set.

The infusion tubing may be primed with 0.9% normal saline solution or may be primed with the drug making sure that no drug is wasted in doing so. Following the infusion, the IV line should be flushed with 0.9% normal saline solution as required to ensure delivery of the full dose.

Details of the dose level and the total dose to be administered will be documented in the source records. For every infusion, the time started and stopped for each infusion rate, volume infused at each rate, total volume infused, the times of any interruptions/decreases, and the reason if an infusion is stopped prematurely should be documented on the Medical Administration Record. .

For the initial infusion, IMGN901 is to be administered at a rate of 1 mg/min for the first 15 minutes. Provided the patient tolerates this rate of infusion, the rate can be increased to 3 mg/min. If patient tolerates the Cycle 1 Day 1 infusion, all subsequent infusions may be delivered at the 3 mg/min rate. Infusion time will vary depending on rate of infusion and may be several minutes to several hours.

### **Management of Potential IMGN901 Infusion Reactions**

Some patients treated with IV infusions of monoclonal antibodies have experienced concurrent infusion-related reactions with signs or symptoms that can be classified as acute allergic/hypersensitivity reactions or cytokine release

syndrome (see NCI CTCAE, version 4.0). The signs and symptoms include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Anaphylaxis might occur at any time during an infusion. In addition, the re-administration of some monoclonal antibodies has been associated with serum sickness-like reactions manifesting 1 to 14 days after drug administration.

Before any infusion is started, appropriate medical personnel, medication (e.g. epinephrine, inhaled beta agonists, antihistamines, and corticosteroids) and other required resources to treat anaphylaxis must be readily available. Patients experiencing a reaction during the administration of study agent should be treated according to institutional guidelines.

The infusion must be stopped immediately if  $\geq$  Grade 2 allergic/hypersensitivity reactions (including drug fever) or  $\geq$  Grade 3 cytokine release syndrome/acute infusion reaction occurs. The Sponsor or designee must be notified within 24 hours of any infusion reaction requiring interruption of study agent.

For a mild or moderate infusion-related reaction, medication with antihistamine (e.g., with diphenhydramine, 25 to 50 mg orally or equivalent) and acetaminophen (650 mg orally or equivalent) may be considered and, if the signs and symptoms have resolved with the above medications, the infusion may be restarted.

If the event is clearly anaphylaxis, then SQ epinephrine (1/1000, 0.3-0.5 mL or equivalent) should be considered. In the case of bronchospasm, inhaled beta agonist also should be considered. The infusion rate may also be lowered if clinically indicated. Patients experiencing an infusion reaction should be observed in the clinic until resolution of the reaction, or until in the Investigator's best judgment, it is considered safe to allow the patient to be discharged. Patients administered antihistamine for the treatment or prevention of infusion reactions should be given appropriate warnings about drowsiness and impairment of driving ability prior to discharge.

**7.9 Contraindications to infusion of IMGN901:** Because of the cytotoxic nature of DM1, healthy volunteers have not been exposed to IMGN901. IMGN901 is contraindicated in:

- Patients with hypersensitivity or anaphylactic reactions to IMGN901 or to any of the excipients.
- Patients who are pregnant or breast-feeding.

#### **7.10 Infusion related reactions:**

Some patients treated with IV infusions of monoclonal antibodies have experienced concurrent infusion-related reactions with signs or symptoms that can

be classified as acute allergic reactions/hypersensitivity reactions or cytokine release syndrome (see National Cancer Institute Common Toxicity Criteria for Adverse Events [NCI-CTCAE], version 4.0, Appendix F). The signs and symptoms include headache, fever, facial flushing, pruritus, myalgia, nausea, chest tightness, dyspnea, vomiting, erythema, abdominal discomfort, diaphoresis, shivers, hypertension, lightheadedness, hypotension, palpitations, and somnolence. Anaphylaxis might occur at any time during an infusion. In addition, the re-administration of some monoclonal antibodies has been associated with serum-sickness-like reactions manifesting one to 14 days after drug administration.

The specific study protocol should be consulted regarding study drug infusions, the prophylactic measures that are recommended to be used for study drug infusions, and the management of the potential infusion/hypersensitivity reactions. If an anaphylactic reaction occurs, investigators are instructed that the infusion should be discontinued immediately and appropriate therapy initiated.

#### **7.11 Dose calculation of IMGN901**

Total dose should be calculated as in the following example:

Subject's Body Surface Area (BSA) x current dose in mg = total dose in mg

\*The dose will be rounded to the nearest multiple of 10 to avoid wastage as each vial contains IMGN901 100 mg

For example, a subject with a BSA of 1.96 receiving a dose of 100 mg/m<sup>2</sup> would be administered 200 mg of IMGN901 (1.96 x 100 mg = 196 mg: rounded to the nearest 10 would be 200 mg).

### **8.0 PATIENT EVALUATION**

Every effort will be made to adhere to the schedule of events and all protocol requirements. Variations in schedule of events and other protocol requirements that do not affect the rights and safety of the patient will not be considered as deviations. Such variations may include laboratory assessments or follow-up visits completed outside of schedule.

#### **8.1 Pre-Treatment Evaluation**

Unless noted otherwise all pretreatment studies should be obtained within 14 days from time of first dose of the study drug administration.

8.1.1 A complete history and physical, concomitant medications and performance status.

8.1.2 CBC, platelet count, differential (differential can be omitted if WBC is  $\leq 0.5 \times 10^9/L$ ).

- 8.1.3 Creatinine, BUN, total bilirubin, ALT, amylase, lipase, AST, creatinine phosphokinase, uric acid, phosphorus, potassium, calcium, magnesium.
- 8.1.4 Pregnancy test (urine/ plasma) in females of childbearing potential, should be performed 72 hours (urine or plasma) before initiation of therapy.
- 8.1.5 Bone marrow aspirate within the last 28 days preceding study initiation. Cytogenetics will be obtained prior to therapy (results from prior analysis can be used for this purpose. For patients who already have an evidence of disease on peripheral blood or on tissue biopsy from another site, the bone marrow may be omitted after discussion and approval with the principal investigator.
- 8.1.6 Confirmation of CD56 expression on bone marrow, peripheral blood or tissue sample (e.g. lymph node sample in patients with BPDCN, or spleen tissue in patients with MF).
- 8.1.7 Baseline measurement of spleen size by palpation and/or ultrasound/CT for patients with myelofibrosis.

## **8.2 Evaluation During Treatment**

- 8.2.1 Physical exam at the start of each cycle ( $\pm$  4 days).
- 8.2.2 CBC, platelet count, differential once weekly ( $\pm$ 4 days) for the first 4 cycles, then every 2-4 weeks (differential can be omitted if WBC is  $\leq 0.5 \times 10^9/L$ ).
- 8.2.3 Lab draw for Creatinine, BUN, sodium, potassium, uric acid, phosphorus, calcium, magnesium, CPK, AST pre dose on course 1 day 1 and post dose on course 1 day 2. Creatinine, BUN, sodium, potassium, total bilirubin, ALT, AST, CPK, amylase, lipase weekly labs ( $\pm$ 4 days) for the first 4 cycles, then every 2-4 weeks.
- 8.2.4 Bone marrow aspiration for differential and PCR for FLT3 on day 21 ( $\pm$ 7 days) of cycle 1, then every 1-3 cycles. Bone marrow tests can be ordered more frequently if mandated by development of peripheral blood counts. No repeat bone marrow is necessary if nonresponse or progressive disease can be unequivocally diagnosed from peripheral blood tests or, in patients with a WBC  $< 0.3$  if the bone marrow test is considered noncontributory by the investigator at any time point.

- 8.2.5 Concomitant medication data will not be collected or entered into the case report form except for concomitant hydroxyurea and intrathecal chemotherapy if these are administered during the first cycle; however, the subject's medication record will contain a list of concomitant medications.
- 8.2.6 For patients that remain on study with no significant toxicity for more than 6 months, subsequent evaluations during study may be modified after discussion with the principal investigator. These include a decrease in frequency of bone marrow aspirations to every 6-12 months (or as clinically indicated), and other laboratory tests to once every cycle.
- 8.2.7 ALL treatments with IMGN901 must be administered at MDACC. The patient is required to stay locally for course one. During the first cycle all the laboratory evaluations will be done at MDACC. Subsequently, the patient may have the laboratory work done at a local clinic and the results reported to the research nurse for the study. The laboratory work done at the local clinic will be forwarded to the patient's attending physician at MDACC or PI of the study, who will sign off on the labs to verify that the results have been reviewed.

### **Outside Physician Participation During Treatment**

- 1. MDACC Physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record
- 2. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's evaluations. It will be made clear in the letter that all treatments with IMGN901 must be administered at MDACC. (Appendix E)
- 3. Changes in drug dose and/or schedule must be discussed with and approved by the MDACC physician investigator, or their representative prior to initiation, and will be documented in the patient record.
- 4. Protocol required evaluations outside MDACC will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MDACC physician, indicating that they have reviewed it.
- 5. A copy of the informed consent, protocol abstract, treatment

schema and evaluation during treatment will be provided to the local physician.

6. Documentation to be provided by the local physician will include progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations.

7. The home physician will be requested to report to the MDACC physician investigator all life threatening events within 24 hours of documented occurrence.

8. All protocol specified follow-up visits will be performed at MDACC.

8.2.8 End of Treatment Visit to be completed 30 days (+/-7 days) after the last dose of study drug. Blood (about 2-3 teaspoons) will be drawn for CBC with differential and platelets and a limited chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT). A bone marrow aspiration may be recommended only if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood. No other procedures or labs will be needed.

8.2.9 Patients with an objective response at completion of active study treatment will be followed for survival at MD Anderson Cancer Center (MDACC) every 3 to 6 months for up to 5 years after completion of active treatment and while still on study. If the patient is unable to return to MDACC the follow-up visits may be conducted via telephone.

Data regarding adverse events will be collected during the study. Protocol specific data will be entered into PDMS/CORE. PDMS/CORE will be used as the electronic case report form for this protocol. Unexpected and related AEs will be recorded in the Case Report Form (CRF). All adverse events should be recorded on the adverse event log with attribution for review. The Principal Investigator will sign and date the AE log per each patient at the completion of each course. Following signature, the AE log will be used as source documentation for the adverse events for attribution.

Treatment may be discontinued for a variety of reasons, including patient withdrawal, investigator decision, and reasons specified by the protocol. Reasons for discontinuation of treatments are described below.

## **9 DISCONTINUATION OF TREATMENT:**

### **9.1 Discontinuation Criteria for Individual Patients**

#### **9.1.1 Patient Withdrawal**

Patients may voluntarily withdraw consent to participate in the clinical study at any time and without giving any reason. Their withdrawal will not jeopardize their relationship with their healthcare providers or affect their future care. Patients may also choose to withdraw from study treatment, but agree to remain in the study for follow-up procedures.

#### **9.1.2 Investigator Discontinuation of Patient**

The investigator may exercise medical judgment to discontinue study treatment if clinically significant changes in clinical status or laboratory values are noted.

#### **9.1.3 Criteria for Protocol-Defined Required Discontinuation of Treatment**

The protocol requires discontinuation of study treatment for the following reasons:

1. Patient requests discontinuation.
2. Unacceptable toxicity that in the opinion of the investigator makes it unsafe to continue therapy.
  1. Clinically significant progressive disease.
  2. Investigator discretion.

#### **9.1.4 Follow-Up at Treatment Discontinuation or Early Withdrawal**

Patients who discontinue treatment for any reason should complete end-of-treatment procedures when possible. End of treatment procedures will include a CBC with differential and platelets and a limited chemistry profile (total bilirubin, serum creatinine, SGPT or SGOT). A bone marrow aspiration may be recommended only if non-response or progressive disease cannot be unequivocally diagnosed from peripheral blood. Although treatment will be discontinued at that time, all patients who do not withdraw consent for follow-up, die, or become lost to follow-up, will remain on study for follow-up evaluations. Subject will be followed for toxicity for at least 30 days after the last protocol treatment. The 30-day follow-up visit will be scheduled as a clinic visits for clinical evaluation and physical examinations. If the patient cannot make it to the MDACC clinic for this visit, the required follow up treatment procedures may be done with a local physician and the records forwarded to MDACC. The research nurse will contact the patient by telephone and get a verbal assessment of the patient's condition. The phone conversation will then be documented in the patient's charts.

#### **9.2 Study Stopping Rules**

The principal investigator and MDACC IND office have the right to terminate this clinical study at any time. The principal investigator and MDACC IND office, as appropriate, will be involved in any decisions regarding terminating the

study, temporarily suspending enrollment, or stopping ongoing treatment with study treatment.

Reasons for terminating the clinical study or a study site's participation include, but are not limited to, the following:

- The incidence or severity of an adverse reaction related to treatment in this study or other studies indicates a potential health hazard to patients
- Patient enrollment is unsatisfactory
- Data recording is significantly inaccurate or incomplete
- Study site personnel are noncompliant with study procedures
- Pattern of noncompliance is observed

### **9.3 Protocol Violations and Deviations**

Protocol violations are defined as significant departures from protocol-required processes or procedures that affect patient safety or benefit potential, or confound assessments of safety or clinical activity. A protocol deviation is a departure from the protocol that does not meet the above criteria. Protocol violations or deviations may be grouped into the following classes:

- Enrollment criteria
- Study activities
- Noncompliance with dose or schedule, including dose calculation, administration, interruption, reduction, or delay; or discontinuation criteria
- Investigational product handling, including storage and accountability
- Informed consent and ethical issues

## **10 CRITERIA FOR RESPONSE**

Criteria for evaluation of response are specified below. The response's will be determined by the treating physician on evaluation of the available data at the recommended time-points and will be documented in the patient notes.

### **A. Acute leukemia, MDS and BPDCN**

Criteria for response in AML and BPDCN will be as per the international working group for AML.<sup>30</sup> There are no specific criteria for response in BPDCN but since it is classified as an acute myeloid malignancy the AML criteria should be applicable. Responders are patients who obtain a Composite Complete Remission Rate (CRc) with or without cytogenetic response, hematologic improvements, and morphologic leukemia-free state. Overall response rate (ORR) is defined as the confirmed remission rate of all complete and incomplete CRs (i.e., CR+ CRp + CRi).

#### **10.1 Complete Remission (CR)**

For patients to be classified as being in CR, they must achieve a morphologic leukemia-free state and must have an ANC  $> 1 \times 10^9/L$  and platelet count  $\geq 100 \times 10^9/L$ , and normal marrow differential with  $< 5\%$  blasts. There should be no evidence of extramedullary leukemia.



## **10.2 Complete Remission with Incomplete Platelet Recovery (CRp)**

For patients to be classified as being in CRp, they must achieve CR except for incomplete platelet recovery ( $< 100 \times 10^9/L$ ).

## **10.3 Complete Remission with Incomplete Hematological Recovery (CRi)**

For patients to be classified as being in CRi, they must fulfill the criteria for CR except for incomplete hematological recovery with residual neutropenia ( $ANC \leq 1 \times 10^9/L$ ) with or without thrombocytopenia (platelet count  $< 100 \times 10^9/L$ ). In addition, patients do not need to be RBC or platelet transfusion independent (modification to Cheson criteria).

## **10.4 Partial Remission (PR)**

For patients to be classified as being in PR, they must have bone marrow regenerating normal hematopoietic cells with evidence of peripheral recovery with no (or only a few regenerating) circulating blasts and with a decrease of at least 50% in the percentage of blasts in the bone marrow aspirate with the total marrow blasts between 5% and 25%.

## **10.5 Morphologic leukemia-free state:**

Bone marrow:  $\leq 5\%$  myeloblasts

## **10.7 Recurrence of Disease**

Relapse after CR is defined as a reappearance of leukemic blasts in the peripheral blood or  $\geq 5\%$  blasts in the bone marrow aspirate not attributable to any other cause or reappearance or new appearance of extramedullary leukemia. Relapse after PR is similarly defined with reappearance of significant numbers of peripheral blasts and an increase in the percentage of blasts in the bone marrow aspirate to  $> 25\%$  not attributable to any other cause or reappearance or new appearance of extramedullary leukemia.

## **10.8 Response measurement**

Response will be measured and defined for primary endpoints within 3 months of therapy or at time off study as the best response obtained with IMGN901 within the first 3 cycles of therapy. Best response is defined to be the best-measured response ( $CRc = CR + CRp + CRi$ , PR, or marrow clearance) post-treatment up to that time. Best response will also be evaluated for the full treatment period using all assessments up to and including treatment discontinuation.

## **B. Myelofibrosis**

For MF refractory to ruxolitinib or JAK-inhibitor therapy, there is no standard of care. The efficacy of IMGN901 will be measured by the overall response rate, defined as a 50% shrinkage in spleen size on manual palpation (or 35% shrinkage in spleen size on imaging examination) and/or a 50% reduction in the total symptom score within 12 weeks of initiation of therapy with IMGN901. These response criteria are based on IWG-MRT criteria for assessment of response in myelofibrosis<sup>31</sup>.

## 11 ADVERSE EVENT REPORTING

- 11.1 Adverse event is any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.

Adverse drug reaction is a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.

Assessing causal connections between agents and disease is fundamental to the understanding of adverse drug reactions. In general, a drug may be considered a contributory cause of an adverse event if, had the drug not been administered, 1) the event would not have happened at all, 2) the event would have occurred later than it actually did, or 3) the event would have been less severe.

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution (e.g. definite, probable, possible, unlikely, unrelated) for each event for all subjects enrolled on the trial.

- 11.2 Adverse Events (AEs) will be evaluated against the most current version of the IMGN901 Investigator Brochure for expectedness. The NCI CTCAE will be used to assess and grade AE severity. All AE assessments will be documented in the medical record. CTCAE version 4.0 will be used. 11.2.1 thru 11.2.3 are exceptions from adverse event reporting:

**11.2.1** Myelosuppression related events (due to disease or leukemia therapy)

**11.2.1.1** febrile or infection episodes not requiring management in the intensive care unit

**11.2.1.2** epistaxis or bleeding except for catastrophic CNS or pulmonary hemorrhage or  $\geq$  grade 3 epistaxis or bleeding

**11.2.2** Disease related events

**11.2.2.1** symptoms associated with anemia

-fatigue

-weakness

-shortness of breath except for grade 4 shortness of breath

**11.2.2.2** electrolyte abnormalities (sodium, potassium, bicarbonate, CO<sub>2</sub>, magnesium)

**11.2.2.3** chemistry abnormalities (LDH, phosphorus, calcium, BUN, protein, albumin, uric acid, alkaline phosphatase, glucose)

**11.2.2.4** coagulation abnormalities

**11.2.2.5** hospitalization for disease specific therapy (induction, maintenance, salvage, or stem cell therapy)

**11.2.2.6** alopecia

**11.2.2.7** bone, joint, or muscle pain

**11.2.2.8** liver function test abnormalities associated with infection or disease progression

**11.2.2.9** disease progression

**11.2.2.10** abnormal hematologic values

**11.2.3** General therapy related events

**11.2.3.1** catheter related events

**11.2.3.2** rash related to antibiotic use

11.3 Abnormal hematologic values will not be recorded on the case report form. For abnormal chemical values, the apogee or nadir (whichever is appropriate) will be reported per course on the case report form.

11.4 Serious Adverse Event Reporting (SAE)

An adverse event (AE) is considered “serious” if, in the view of either the investigator or the IND Medical Monitor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate

risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

**11.4.1** Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

All cases of IMGN901 overdose (defined as accidental or intentional ingestion of any dose of the product that is considered excessive and medically important) must be reported as an SAE to the MDACC IND office on the SAE Form. Determination of seriousness will be reached in consultation with the PI.

Pregnancy alone is not considered an AE. However, if a patient becomes pregnant or causes a pregnancy during treatment or within 4 weeks of ending treatment, even if the subject is withdrawn from the study, the pregnancy must be reported immediately on the MD Anderson SAE Form to the MDACC IND office within 24 hours of the Investigator's knowledge of the pregnancy. The investigator should abide by necessary regulation for medical release from a female partner of a male subject prior to obtaining follow up. The investigator will follow the pregnancy to term or termination, will collect data on both the maternal and fetal outcome and will report all outcomes as a follow-up report to the initial pregnancy notification to the MDACC IND office in accordance with Section 11.4.3.

Notwithstanding, all pregnancy outcomes that meet the regulatory definition of serious (i.e. spontaneous abortion, neonatal death, congenital anomaly in an aborted fetus or neonate) will be reported

on the MD Anderson SAE Form to the MDACC IND office within 24 hours of Investigator knowledge of the outcome.

Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Medical Monitor.

- All events occurring during the conduct of a protocol that meet the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Unanticipated Adverse Events for Drugs and Devices.” Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the MDACC IND Office, regardless of attribution (within 5 working days of knowledge of the event).
- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 30-day time period that is related to the study treatment must be reported to the MDACC IND Office. This may include the development of a secondary malignancy.
- Immunogen Inc. is providing the IMGN901 for this study.

#### **11.4.2 Reporting to FDA**

Serious adverse events will be forwarded to FDA by the MDACC IND office (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the MDACC IND office guidelines, and Institutional Review Board policy.

#### **11.4.3 Investigator Communication with Supporting Companies**

To protect human subjects, entities that provide the IMGN901 drug to or receive the IMGN901 drug from other entities will share safety information with each other. To that end, the PI and the research team will provide copies of IND Safety Reports within 24 hours of submission to ImmunoGen, Inc. Pharmacovigilance and, upon request, the Safety Officer of other IMGN901 entities. In turn, the MD Anderson IND office (or study Principal Investigator) will receive IND Safety Reports originating from other entities using IMGN901. Each entity will provide notification when their study is closed and no further safety data will be forthcoming

## **12 STATISTICAL CONSIDERATIONS**

The primary objectives of the study are to evaluate the overall response rate to IMGN901 in patients with CD56 expressing hematological malignancies including but not limited to relapsed/refractory leukemia, myelofibrosis refractory to ruxolitinib or JAK-inhibitor therapy, and BPDCN. A response and toxicity summary for each treatment cohort (1, 2 and 3) will be submitted to the IND Medical Monitor per the guidelines found in the statistical section 12.0.

### **Cohort 1 (Relapsed/refractory leukemia)**

The primary objective of cohort 1 is to assess the efficacy of treatment of IMGN901 in CD56 expressing hematological malignancies including but not limited to AML, high-risk MDS, natural-killer leukemia, acute lymphoblastic leukemia, accelerated and blast-phase CML who have failed prior therapy or for which no standard therapy exists. We anticipate that the majority of the patients in this cohort will be relapsed/refractor AML. The efficacy of IMGN901 will be measured by the ORR, defined as CR (complete remission) + CRp (complete remission with incomplete platelet recovery) + CRi (complete remission with incomplete count recovery) within 3 cycles of therapy with IMGN901 in patients with CD56 expressing leukemia's (defined in section 10.0) who have failed prior therapy or for which no standard therapy exists.

We anticipate that the majority of patients in this cohort will be relapsed/refractory AML. The historical data suggested the ORR to current standard salvage treatment is 30%. The target ORR with the experimental treatment is 50%. The regimen of the IMGN901 will be considered worthy of

further investigation if it elicits an increase in ORR to 50% with acceptable toxicity. A >30% therapy related non-hematological grade 3/4 toxicity rate is considered unacceptable. Thus, interim monitoring rules, assuming the prior distributions above, were constructed that meet the following two conditions,

1) Stop if  $\text{Prob}[p(\text{ORR}, E) > 0.50 \mid \text{data}] < 0.05$ , or

2) Stop if  $\text{Prob}[p(\text{TOX}, E) > 0.30 \mid \text{data}] > 0.95$ ,

where  $P(\text{ORR}, E)$  and  $P(\text{TOX}, E)$  are the true ORR and toxicity rates for the IMGN901. The first rule provides for stopping the study if the data suggest that it is unlikely (i.e., probability < 5%) that ORR rate of the IMGN901 is greater than the ORR rate of standard treatment by 20%. The second condition will stop the study early if excessive therapy-related non-hematological grade 3/4 toxicity (>30%) is highly probable (i.e., probability >95%) for the IMGN901. Monitoring for toxicity and futility will not begin until 5 patients have been evaluated, and cohort size for future evaluations is 5.

The monitoring rule for the toxicity rate, based on these assumptions and monitoring conditions above is found in Table 4. For example, accrual will cease if 4 or more patients experience toxicities among the first 5 patients.

Table 4. Stop accrual if the number of drug-related non-hematological grade 3/4 toxicities is greater than or equal to indicated (i.e., # patients with toxicities) among the number of patients evaluated				
# patients evaluated	5	10	15	20
# patients with toxicities	4-5	6-10	8-15	Always stop with this many patients

Monitoring the ORR rate, based on the above assumptions and monitoring conditions is found in Table 5. For example, accrual will cease if less than 1 patient experience an overall response within 3 cycles of IMGN901 in the first 15 patients treated. If <1/15 of the initially treated patients achieve response we will consider alternate dosing schedule with IMGN901 administered on days 1,8,15 of a 21-day cycle. This will be done in discussion with the MDACC IND office, FDA and the IRB. Rules for dose-interruption and dose-adjustment will remain as defined in the protocol.

Table 5. Stop accrual if the number with overall response is less than or equal to indicated (i.e., # patients with overall response) among the number of patients evaluated				
# patients evaluated	5	10	15	20
# patients with overall response	0	0-2	0-4	Always stop with this many patients

Multic Lean Desktop (version 2.1.0) was used to generate the toxicity and futility stopping boundaries and the OC table (Table 6). In order to utilize the software for the design, a response constant rate of 0.30 and beta (0.6, 1.4) priors and delta of 20% were assumed for the standard treatment response distribution and experimental treatment response prior distribution, respectively. In addition, a 30% toxicity constant rate and beta (0.6, 1.4) priors were assumed for the standard treatment toxicity constant rate and experimental treatment toxicity prior distribution, respectively.

The probability of stopping the study early if the true ORR of the IMGN901 was 50% and the true toxicity rate was 30% was 11.3%. Probabilities of stopping early for high true toxicity rates (i.e., 50%) were 63.7% when the true ORR was 30% and 57.3% when true ORR rate was 50%.

Table 6. Operating characteristics for simultaneous monitoring response and toxicity rates for patients treated with IMGN901 treatment		
True Toxicity Rate	True ORR	Prob(stop the trial early)
0.10	0.30	0.5725
	0.40	0.2778
	0.50	0.0972
	0.60	0.0244
	0.70	0.0045
0.20	0.30	0.5779
	0.40	0.2870
	0.50	0.1086
	0.60	0.0367
	0.70	0.0171
0.30	0.30	0.6083
	0.40	0.3384
	0.50	0.1730
	0.60	0.1062
	0.70	0.0881
0.40	0.30	0.6892
	0.40	0.4751
	0.50	0.3438
	0.60	0.2908
	0.70	0.2764
0.50	0.30	0.8113
	0.40	0.6812
	0.50	0.6014
	0.60	0.5693
	0.70	0.5605

## Cohort 2 (Myelofibrosis refractory to JAK-inhibitor therapy)



The primary objective of the cohort 2 is to assess the efficacy of IMGN901 in MF patients who are refractory to JAK-inhibitor therapy. No standard of care exists for such patients. The efficacy of IMGN901 will be measured by the overall response rate, defined as a 50% shrinkage in spleen size on manual palpation (or 35% shrinkage in spleen size on imaging examination) and/or a 50% reduction in the total symptom score within 3 cycles of IMGN901 therapy.

### *Futility Monitoring*

Historical data on similar patients shows an ORR of 20%. The target response rate is 35%. Given this, we will stop enrollment into this cohort if the observed patients' data suggest that:

$$\Pr(p(\text{ORR}, E) > 0.35 | \text{data}) < 0.025$$

where  $P(\text{ORR}, E)$  is the overall response rate (ORR) for the treatment. That is, if at any time during the study we determine that there is a less than 2.5% chance that ORR rate of the IMGN901 is greater than the ORR rate of standard treatment by 15% we will stop enrollment to this cohort.  $P(\text{ORR}, E)$  is assumed to follow a prior of Beta (0.4, 1.6). The stopping boundaries for ORR, based on these assumptions and monitoring conditions are found in Table 7. We will apply these stopping boundaries continuously starting from the first patient in cohorts of 10. For example, accrual will cease if 0 patients experiences overall response among the first 10 patients treated within 3 cycles of therapy with IMGN901. The operating characteristics are summarized in Table 8.

Table 7. Stopping boundaries for ORR

Number of patients evaluated for overall response	10	20
Number of patients with overall response (i.e., CR, CRp or CRi) is less than or equal to	0 – 1	2-4

Table 8. Operating characteristics for monitoring ORR

True overall Response Rate	Early Stopping Probability	Average number of patients treated
0.20	0.3758	16
0.25	0.2440	18
0.30	0.1493	19
0.35	0.0860	19
0.40	0.0464	20
0.45	0.0233	20

### *Toxicity Monitoring*

In addition, we will monitor toxicities. The probability of toxicity is denoted by  $P(\text{TOX}, E)$ . We assume  $P(\text{TOX}, E) \sim \text{beta}(0.6, 1.4)$ . Our stopping rule is given by the following probability statement:  $\Pr(P(\text{TOX}, E) > 0.30 \mid \text{data}) > 0.85$ . That is, we will stop the study if, at any time during the study, we determine that there is more than 90% chance that the toxicity is more than 30%. The stopping boundaries for toxicities, based on these assumptions and monitoring conditions is found in Table 9. We will apply the toxicity monitoring rule in cohort size of 5, starting from the 1<sup>st</sup> patient. For example, accrual will cease if all 3 patients experience toxicities among the first 5 patients treated. The operating characteristics are summarized in Table 10.

Table 9. Stopping boundaries for toxicity monitoring

The number of patients evaluated for toxicities	5	10	15	20
The number of patients with toxicities is greater than or equal to	3	5	7	9

Table 10. Operating characteristics for toxicity monitoring

True overall Toxicity Rate	Early Stopping Probability	Average number of patients treated
0.10	0.0089	20
0.20	0.0787	19
0.30	0.2607	17
0.40	0.5173	14
0.50	0.7846	10

### Cohort 3 (BPDCN)

The primary objective of the cohort 3 is to assess the efficacy of IMGN901 in patients with a confirmed pathological diagnosis of BPDCN. The efficacy of IMGN901 will be measured by the ORR, defined as CR (complete remission) + CRp (complete remission with incomplete platelet recovery) + CRi (complete remission with incomplete count recovery) (as specified in section 10.0) within 3 cycles of therapy with IMGN901.

#### *Futility Monitoring*

Historical data on similar patients show a ORR of 20%. The target response rate is 35%. Given this, we will stop enrollment into this cohort if the observed patients' data suggest that:

$$\Pr(p(\text{TOX}, E) > 0.35 \mid \text{data}) < 0.025$$

where  $p(\text{ORR}, E)$  is the overall response rate (ORR) for the treatment. That is, if at any time during the study we determine that there is a less than 2.5% chance that ORR rate of the IMGN901 is greater than the ORR rate of standard treatment by 15% we will stop enrollment to this cohort.  $P(\text{ORR}, E)$  is assumed to follow a prior of Beta (0.4, 1.6). The stopping boundaries for ORR, based on these assumptions and monitoring conditions are found in Table 11. We will apply these stopping boundaries continuously starting from the first patient and in cohorts of 10. For example, accrual will cease if less than 1 patients experiences overall response among the first 10 patients treated within 3 cycles of therapy with IMGN901. The operating characteristics are summarized in Table 12.

Table 11. Stopping boundaries for ORR

Number of patients evaluated for overall response	10	20
Number of patients with overall response (i.e., CR, CRp or CRi) is less than or equal to	0-1	2-4

Table 12. Operating characteristics for monitoring ORR

True overall Response Rate	Early Stopping Probability	Average number of patients treated
0.20	0.3758	16
0.25	0.2440	18
0.30	0.1493	19
0.35	0.0860	19
0.40	0.0464	20
0.45	0.0233	20

### *Toxicity Monitoring*

In addition, we will monitor toxicities. The probability of toxicity is denoted by  $P(\text{TOX}, E)$ . We assume  $P(\text{TOX}, E) \sim \text{beta}(0.6, 1.4)$ . Our stopping rule is given by the following probability statement:  $\Pr(P(\text{TOX}, E) > 0.30 \mid \text{data}) > 0.85$ . That is, we will stop the study if, at any time during the study, we determine that there is more than 90% chance that the toxicity is more than 30%. The stopping boundaries for toxicities, based on these assumptions and monitoring conditions is found in Table 13. We will apply the toxicity monitoring rule in cohort size of 5, starting from the 1<sup>st</sup> patient. For example, accrual will cease if all 3 patients experience toxicities among the first 5 patients treated. The operating characteristics are summarized in Table 14.

Table 13. Stopping boundaries for toxicity monitoring

The number of patients evaluated for toxicities	5	10	15	20
The number of patients with toxicities is greater than or equal to	3	5	7	9

Table 14. Operating characteristics for toxicity monitoring

True overall Toxicity Rate	Early Stopping Probability	Average number of patients treated
0.10	0.0089	20
0.20	0.0787	19
0.30	0.2607	17
0.40	0.5173	14
0.50	0.7846	10

### Statistical Analysis Plan

All patients who received any dose of the study agent will be included in the analysis for efficacy and safety. Demographic/clinical characteristics (including duration of response) and safety data of the patients will be summarized using descriptive statistics such as mean, standard deviation, median and range. For the primary efficacy analysis, we will estimate the ORR for the IMGN901, along with the 95% confidence interval. Patients who drop out of the study before completing all the cycles will be treated as “failures” for the primary analysis. Overall response rate (ORR) during the study period will also be presented with the 95% confidence interval. The association between ORR and patient’s clinical characteristics will be examined by Wilcoxon’s rank sum test or Fisher’s exact test, as appropriate. Toxicity type, severity and attribution will be summarized for each patient using frequency tables. The distribution of time-to-event endpoints including duration of response, overall survival and progression free survival will be estimated using the method of Kaplan and Meier. Comparisons of time-to-event endpoints by important subgroups will be made using the log-rank tests. Correlation analysis (such as logistic regression analysis) will be conducted to determine the relationship between IMGN901 and other gene expression and clinical response.

### **13.0 REFERENCES:**

1. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin. 2013;63: 11-30.

2. Heerema-McKenney A, Arber DA. Acute myeloid leukemia. *Hematol Oncol Clin North Am.* 2009;23: 633-654.
3. Appelbaum FR, Gundacker H, Head DR, et al. Age and acute myeloid leukemia. *Blood.* 2006;107: 3481-3485.
4. Kantarjian HM. Therapy for elderly patients with acute myeloid leukemia: a problem in search of solutions. *Cancer.* 2007;109: 1007-1010.
5. Kantarjian H, O'Brien S, Cortes J, et al. Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome: predictive prognostic models for outcome. *Cancer.* 2006;106: 1090-1098.
6. Estey EH. Treatment of relapsed and refractory acute myelogenous leukemia. *Leukemia.* 2000;14: 476-479.
7. Ravandi F, Cortes J, Faderl S, et al. Characteristics and outcome of patients with acute myeloid leukemia refractory to 1 cycle of high-dose cytarabine-based induction chemotherapy. *Blood.* 2010;116: 5818-5823; quiz 6153.
8. Stanisic S, Kalaycio M. Treatment of refractory and relapsed acute myelogenous leukemia. *Expert Rev Anticancer Ther.* 2002;2: 287-295.
9. Seymour JF, Pierce SA, Kantarjian HM, Keating MJ, Estey EH. Investigation of karyotypic, morphologic and clinical features in patients with acute myeloid leukemia blast cells expressing the neural cell adhesion molecule (CD56). *Leukemia.* 1994;8: 823-826.
10. Mann KP, DeCastro CM, Liu J, Moore JO, Bigner SH, Traweek ST. Neural cell adhesion molecule (CD56)-positive acute myelogenous leukemia and myelodysplastic and myeloproliferative syndromes. *Am J Clin Pathol.* 1997;107: 653-660.
11. Legrand O, Perrot JY, Baudard M, et al. The immunophenotype of 177 adults with acute myeloid leukemia: proposal of a prognostic score. *Blood.* 2000;96: 870-877.
12. Chang H, Brandwein J, Yi QL, Chun K, Patterson B, Brien B. Extramedullary infiltrates of AML are associated with CD56 expression, 11q23 abnormalities and inferior clinical outcome. *Leuk Res.* 2004;28: 1007-1011.
13. Junca J, Garcia-Caro M, Granada I, et al. Correlation of CD11b and CD56 expression in adult acute myeloid leukemia with cytogenetic risk groups and prognosis. *Ann Hematol.* 2014;93: 1483-1489.
14. Di Bona E, Sartori R, Zambello R, Guercini N, Madeo D, Rodeghiero F. Prognostic significance of CD56 antigen expression in acute myeloid leukemia. *Haematologica.* 2002;87: 250-256.
15. Baer MR, Stewart CC, Lawrence D, et al. Expression of the neural cell adhesion molecule CD56 is associated with short remission duration and survival in acute myeloid leukemia with t(8;21)(q22;q22). *Blood.* 1997;90: 1643-1648.
16. Yang DH, Lee JJ, Mun YC, et al. Predictable prognostic factor of CD56 expression in patients with acute myeloid leukemia with t(8 : 21) after high dose cytarabine or allogeneic hematopoietic stem cell transplantation. *Am J Hematol.* 2007;82: 1-5.
17. Murray CK, Estey E, Paietta E, et al. CD56 expression in acute promyelocytic leukemia: a possible indicator of poor treatment outcome? *J Clin Oncol.* 1999;17: 293-297.
18. Raspadori D, Damiani D, Lenoci M, et al. CD56 antigenic expression in acute myeloid leukemia identifies patients with poor clinical prognosis. *Leukemia.* 2001;15: 1161-1164.

19. Mehta J, Wang H, Iqbal SU, Mesa R. Epidemiology of myeloproliferative neoplasms in the United States. *Leuk Lymphoma*. 2014;55: 595-600.
20. Gangat N, Caramazza D, Vaidya R, et al. DIPSS plus: a refined Dynamic International Prognostic Scoring System for primary myelofibrosis that incorporates prognostic information from karyotype, platelet count, and transfusion status. *J Clin Oncol*. 2011;29: 392-397.
21. Mesa RA, Mehta J, Wang HW, et al. Epidemiology of Myeloproliferative Disorders in US - a Real World Analysis. *Blood*. 2012;120.
22. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med*. 2012;366: 799-807.
23. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med*. 2012;366: 787-798.
24. Feng B, Verstovsek S, Jorgensen JL, Lin P. Aberrant myeloid maturation identified by flow cytometry in primary myelofibrosis. *Am J Clin Pathol*. 2010;133: 314-320.
25. Cota C, Vale E, Viana I, et al. Cutaneous manifestations of blastic plasmacytoid dendritic cell neoplasm-morphologic and phenotypic variability in a series of 33 patients. *Am J Surg Pathol*. 2010;34: 75-87.
26. Petrella T, Bagot M, Willemze R, et al. Blastic NK-cell lymphomas (agranular CD4+CD56+ hematodermic neoplasms): a review. *Am J Clin Pathol*. 2005;123: 662-675.
27. Woll PJ, O'Brien M, Fossella F, et al. Phase I Study of Lorvotuzumab Mertansine (Imgn901) in Patients with Cd56-Positive Solid Tumours. *Annals of Oncology*. 2010;21: 175-176.
28. Chanan-Khan A, Wolf JL, Garcia J, et al. Efficacy Analysis From Phase I Study of Lorvotuzumab Mertansine (IMGN901), Used as Monotherapy, In Patients with Heavily Pre-Treated CD56-Positive Multiple Myeloma - A Preliminary Efficacy Analysis. *Blood*. 2010;116: 819-819.
29. Berdeja JG, Hernandez-Ilizaliturri F, Chanan-Khan A, et al. Phase I Study of Lorvotuzumab Mertansine (LM, IMGN901) in Combination with Lenalidomide (Len) and Dexamethasone (Dex) in Patients with CD56-Positive Relapsed or Relapsed/Refractory Multiple Myeloma (MM). *Blood*. 2012;120.
30. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol*. 2003;21: 4642-4649.
31. Tefferi A, Cervantes F, Mesa R, et al. Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report. *Blood*. 2013;122: 1395-1398.